

Genelex Corporation

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Comprehensive, personalized medication management and pharmacogenetic testing are important existing opportunities to reduce adverse medication events and improve overall healthcare outcomes. A primary barrier to the adoption of personalized pharmacology is the inadequacy of existing patient records, drug interaction tools and the 'interpretation gap' – the lack of physician decision support tools needed to interpret DNA test reports. GeneMedRx, an algorithm-driven, gene–drug interaction software closes this gap. It helps physicians optimize medication regimens by correlating the genetic makeup of the patient with all the medicines they are taking. Portable personal health records created by GeneMedRx are the core product required for a much needed comprehensive program of personalized medication management.

Genelex Corporation is a pioneer in quality assured and consumer-oriented DNA testing. First, in the 1990s for forensic and paternity testing, since 2000, in genetic testing for the key cytochrome P450 drug metabolizing enzymes, 2D6, 2C9 and 2C19, and now in providing GeneMedRx. GeneMedRx is the most comprehensive software tool available for the detection of drug interactions, interpretation of pharmacogenetic DNA test results, and overall management of patient medication regimens. Incorporated in Washington State, USA in 1987, Genelex is privately held and seeks capital investment, strategic partners and licensing opportunities to expand GeneMedRx's utility as a comprehensive platform for personalized medication management. Projects at various stages include expansion of market reach, development and incorporation of proprietary new algorithms, genetic test development and integration with complementary software programs.

Wider use of GeneMedRx, especially when DNA test results are available, has the potential to greatly reduce the epidemic of adverse drug outcomes, described by the US FDA as a major public health problem (Box 1). Adverse outcomes to 'properly' prescribed medicines are the third or fourth leading cause of death in the USA if we add treatment failures to overdose toxicity caused by undetected drug interactions and patient genotypes [1]. Underlying this problem is the fractured nature of medication management because of the lack of a central repository for patient information, large numbers of patients taking multiple medications, inadequacies of the most widely used drug interaction detection sys-

tems and a generalized failure to apply the latest scientific knowledge to clinical medicine [2].

In 2000, Genelex was clearly ahead of the market for pharmacogenetic testing. Now, in 2008, personalized medication management, based on DNA testing of the cytochrome P450s and other drug metabolizing enzymes, is approaching critical mass to improve the effectiveness and safety of medicines. Various clinical studies demonstrating positive outcomes for specific drug–gene sets are published or underway, and the FDA is actively relabeling medicines to describe and recommend DNA testing (Table 1). Many scientists believe that the application of pharmacogenetic technologies to clinical medicine will lead to dramatic reductions in the morbidity, mortality and monetary costs of adverse medication outcomes [3].

The three primary drug metabolizing enzymes, CYP2D6, CYP2C9 and CYP2C19 are essential for the normal metabolism of approximately one-half of the 200 most frequently prescribed medicines. The genes for these enzymes are among the most polymorphic known. Generally underappreciated, this exceptional variation accounts for many of the individual and population differences in medication response observed by physicians in everyday practice. Medications on the top 200 list that require these often altered and missing pathways for normal functioning, are eight times more likely to be reported as causing adverse drug events, when compared with a random selection from the top 200 list [4].

Genelex currently markets GeneMedRx and DNA testing for *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP1A2*, vitamin K epoxide reductase complex

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Box 1. Adverse medication outcomes problem.

Incidence

- Adverse drug reactions (ADRs) are the fourth to sixth greatest killer in US with more than 100,000 deaths; and 2.2 million serious adverse reactions per year according to a 1998 report [1]. This study is a meta-analysis of 39 research reports published from 1966 to 1996.
- Hospitalized psychiatric patients who are poor metabolizers cost US\$4,000–6,000 more in medical care compared with patients with an average metabolizer genotype. All antidepressants and antipsychotic medicines are processed by enzymes with a high incidence of poor metabolizers [18].
- A total of 59% of most commonly cited drugs in ADR studies are processed by enzymes with genes known to have poor metabolizer variants. This is compared with 7% of a random selection of the top selling drugs [4].

Financial consequences

- US\$1.77 billion in added health care costs per year [19].
- Health maintenance organizations (HMOs) spend more treating ADRs than on drugs.
- ADRs are the cost leader for malpractice payouts.
- Up to a third of drug prescriptions are not needed and are therefore wasted.

subunit 1 (*VKORC1*), *NAT2*, *DPD*, and *UGT1A1* to consumers, healthcare providers, and pharmaceutical companies conducting clinical trials. These tests are used in specific gene–drug combinations, such as for tamoxifen efficacy, warfarin dosing, irinotecan toxicity avoidance and for overall personalized medication management [5,6,7].

GeneMedRx

In development for more than a decade, the GeneMedRx software is driven by a drug metabolism based algorithm. It spans the ‘interpretation gap’ by providing actionable information to prescribers who have pharmacogenetic test

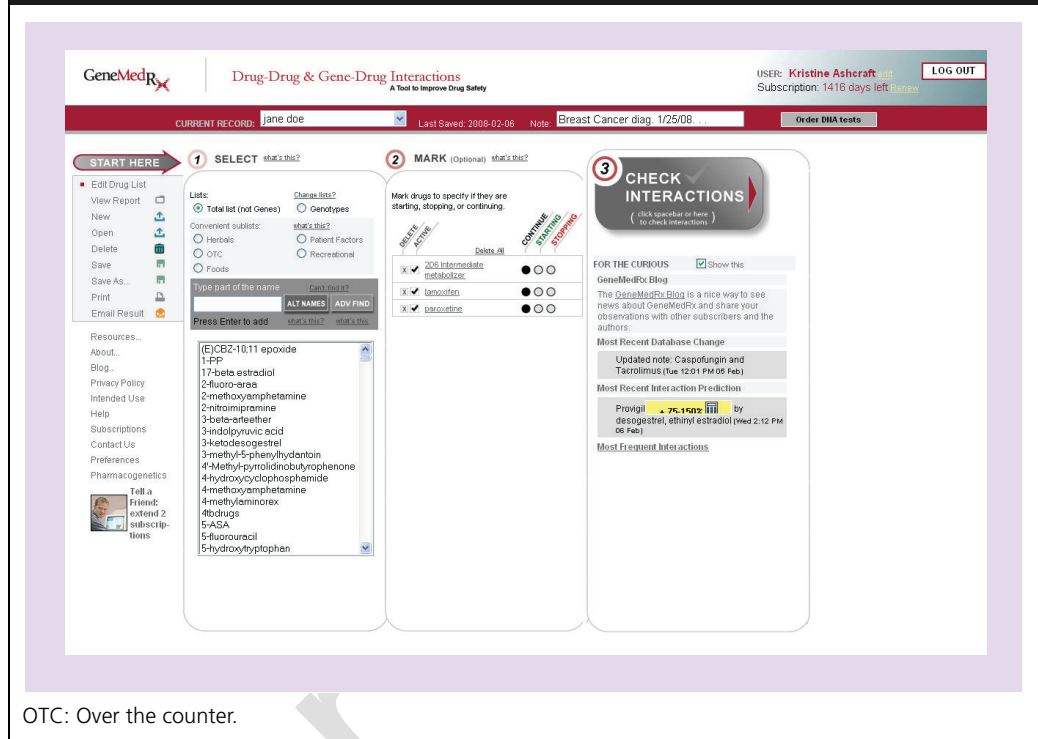
results available. Incorporating the body of drug metabolism knowledge built on decades of research also sets GeneMedRx apart from other drug interaction softwares. The standard approach is to depend exclusively on clinical reports which fail to lead to an understanding of why there is a drug interaction and don’t allow for multiple drug–drug or drug–gene comparisons. Clinical reports also may be conflicting and report only the most serious and obvious problems. Almost none take into account patient genetic variation. The result is that most drug interactions go undetected and untreated (Figure 1).

Table 1. Pharmacogenetic FDA label changes.

| Drug | Labeling date | Polymorphic DME | Summary |
|---|---------------|------------------|--|
| Strattera (atomoxetine) | March (2003) | CYP2D6 | PMs have a 10× greater AUC, 5× greater peak level and the $t_{0.5}$ increases from 5 to 25 h. Dosage reduction is recommended when also taking CYP2D6 inhibitors. |
| Mellaril (thioridazine) | July (2003) | CYP2D6 | Contraindicated in the approximately 7% of US patients who are CYP2D6 PMs. |
| Tamoxifen | Pending | CYP2D6 | Tamoxifen is a prodrug and must be activated into endoxifen by CYP2D6 therefore CYP2D6 PMs will not receive therapeutic benefit from tamoxifen. |
| Vfend (voriconazole) | April (2004) | CYP2C19 | PMs have a 4× greater AUC and IMs a 2× greater AUC. |
| Coumadin (warfarin) | August (2007) | CYP2C9 VKORC1 | Genotyping these two genes allows the maintenance dose to be predicted to within ± 1 mg/day. |
| Purinethol (azathioprine) (6-mercaptopurine) | July (2004) | TPMT | Patients with little or no inherited TPMT activity require substantial dose reduction to prevent rapid bone marrow suppression. |
| Camptosar (irinotecan) | March (2005) | UGT1A1 | Gilbert syndrome patients, who are homozygous for the <i>UGT1A1</i> *28 variation require reduction in the starting dose by one level to prevent severe neutropenia. |

AUC: Area under the curve; DME: Drug metabolizing enzymes; IM: Intermediate metabolizer; PM: Poor metabolizer; $t_{0.5}$: Half life.

Figure 1. GeneMedRx interaction entry screen allows for input of genotypes, multiple medications, herbals, OTCs, foods, patient factors and recreational drugs to assess the risk of interactions.



OTC: Over the counter.

Features and benefits of GeneMedRx include:

- Simultaneously analyzes and reports multiple drug and gene interactions for each patient. Reports may be saved printed and emailed, providing a single, portable repository of patient medication regimens.
- Generates reports based on knowledge of drug metabolism and pharmacogenetics in addition to clinical reports. Most subscribers use it primarily as a drug interaction analysis tool (Figure 2).
- Runs ‘what if’ scenarios around starting and stopping medications indicating the time course of expected effects.
- Suggests alternative, potentially safer medicines when an interaction is predicted (Figure 3).
- Built on more than 4500 individually curated research reports. Reports are immediately accessible by computer links to PubMed and other primary sources.
- Includes more than 4000 prescription drugs, over-the-counter medicines, herbal preparations and a variety of other patient factors that can lead to adverse drug interactions.

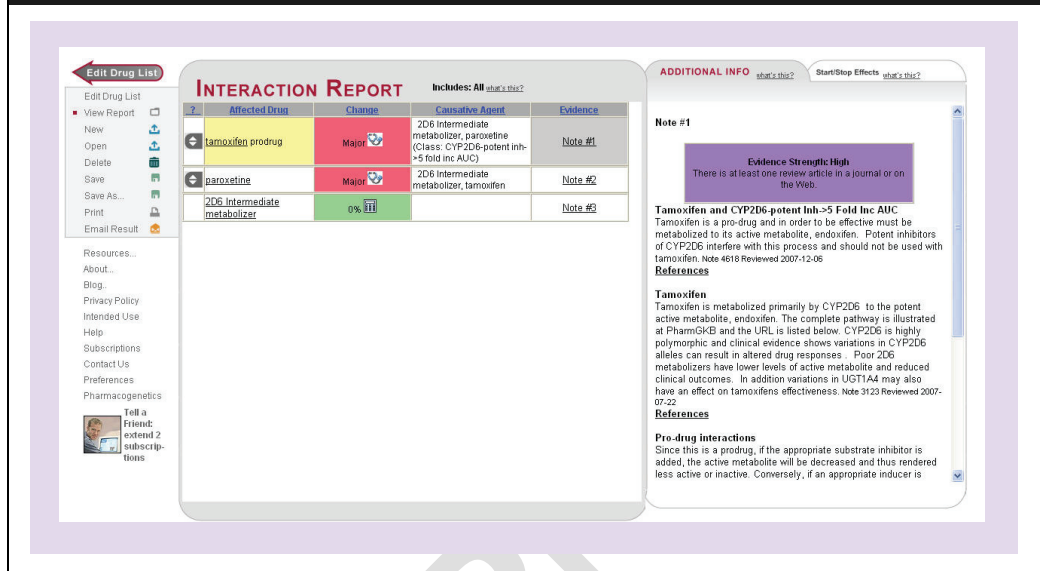
Since 1996, physicians, pharmacists and computer scientists have been creating and updating

the database and honing the proprietary prediction algorithm. GeneMedRx is available on an annual subscription basis for both professionals and consumers. A password protected, secure account is established for each DNA testing client that is the basis for professional interpretation of DNA test results. GeneMedRx is also in various stages of integration into existing electronic health management and records systems. The goal for GeneMedRx is to make it available as a personalized medication management software platform for a variety of healthcare markets and applications. These include electronic medical records, pharmaceutical and other benefit managers, healthcare plans, corporate self-insurers and insurance companies other drug interaction softwares, clinical laboratories and consumer oriented web portals.

Tamoxifen, CYP2D6 & antidepressants

The story of tamoxifen pharmacogenetics illustrates the need for comprehensive medication management that includes pharmacogenetic testing (Box 2). Cytochrome P450 2D6, the enzyme important to test for tamoxifen efficacy, is also important for the metabolism and action of antidepressants, the opioid pain medications

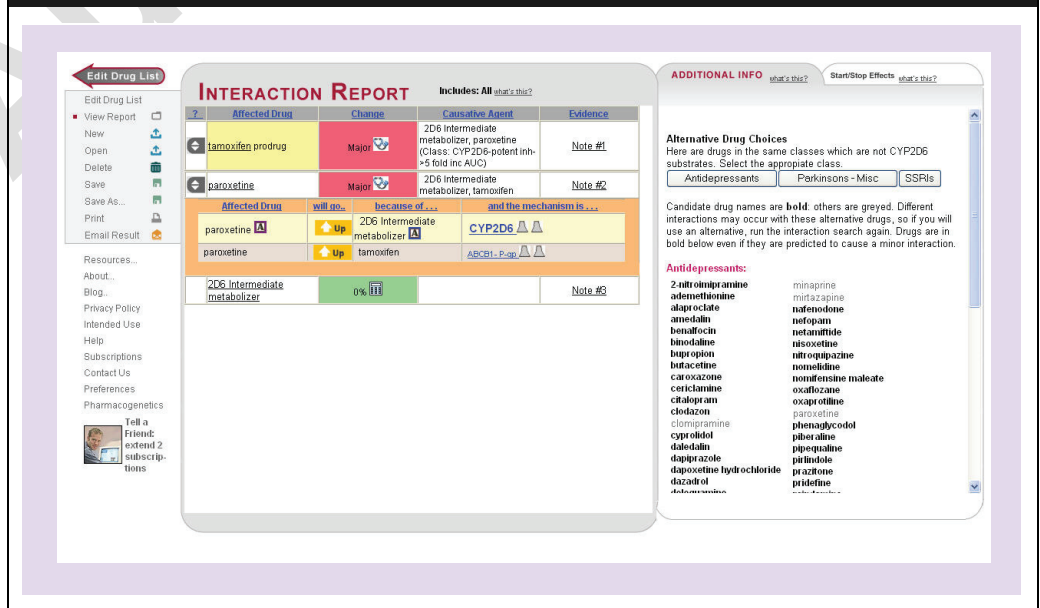
Figure 2. GeneMedRx interaction report for tamoxifen, paroxetine and 2D6 intermediate metabolizer status that predicts the reduction in tamoxifen efficacy for this combination.



and several other classes of medicines that breast cancer patients on tamoxifen also may be taking. Approximately 500,000 women are prescribed tamoxifen to treat and prevent the recurrence of estrogen receptor (ER) positive breast cancer. Out of the approximately 120,000 new patients diagnosed with ER positive breast cancer each

year, 42,000 are predicted to fail tamoxifen treatment. Many of these individuals are CYP2D6 poor metabolizers and are unable to convert tamoxifen into its active metabolite, endoxifen which is 30–100 times more effective as a cancer treatment than tamoxifen [8]. Two year relapse free survival is 68% in patients receiving

Figure 3. GeneMedRx interaction report for tamoxifen, paroxetine and 2D6 intermediate metabolizer status with the mechanism details displayed for the paroxetine interaction and the alternative options selected to display alternative medications that do not rely on the CYP2D6 pathway for metabolism.



Box 2. Tamoxifen and CYP2D6

Tamoxifen is currently the most common treatment to prevent the recurrence of breast cancer in postmenopausal women.

More than 500,000 women take tamoxifen, with approximately 120,000 new prescriptions written each year.

Cytochrome P450 2D6 is responsible for converting tamoxifen to endoxifen which is 30–100× for effective in preventing the recurrence of breast cancer.

'Hot flashes', a common side effect of tamoxifen, are often treated with selective serotonin reuptake inhibitors of which many are potent 2D6 inhibitors that reduce conversion to endoxifen.

Up to 35% of women with estrogen receptor positive breast cancer may fail tamoxifen treatment, because of drug interactions and their genetic make-up [8].

tamoxifen who are 2D6 poor metabolizers and 98% for patients who are 2D6 normal metabolizers [9,10]. Patients who are found to be 2D6 poor metabolizers can be placed on alternative therapies such as aromatase inhibitors.

Thoughtful medication management is important for tamoxifen-treated patients who are CYP2D6 normal metabolizers. They become 2D6 poor metabolizers by phenoconversion when co-administered 2D6 inhibitors. 'Hot flashes,' a common side effect of tamoxifen, is typically treated with selective serotonin reuptake inhibitors (SSRI) antidepressants such as Prozac® (fluoxetine), Paxil® (paroxetine) or Zoloft® (sertraline), all notoriously potent 2D6 inhibitors. Individuals who are 2D6 normal metabolizers but receiving a potent 2D6 inhibitor have 58% lower endoxifen levels than 2D6 normal metabolizers not receiving a 2D6 inhibitor [11]. Co administration of opioid analgesics, β-blockers, non-SSRI psychiatric medicines are based on their metabolism to result in similar interactions and outcomes.

Widespread genotyping and analysis of patient overall medication regimens could reduce the failure rate of tamoxifen treatment in ER positive

breast cancer patients from 35% to less than 10%. That amounts to more than 100,000 lives in the USA.

Warfarin (Coumadin®) & DNA testing

Described in an August 2007 re-label of Coumadin, warfarin dosing based on genetics, combines tests for two genes *CYP2C9*, which metabolizes warfarin, and *VKORC1*, which encodes the enzyme that is its site of action. The American Enterprise Institute (AEI)/Brookings Joint Center for Regulatory Studies speculates that, on average, routine DNA testing of 2C9 and VKORC1 in warfarin patients, at a cost of US\$550 per patient, could prevent 85,400 bleeding events, 17,100 strokes and save US\$1.13 billion dollars annually [12]. In August 2007 the FDA, acting on advice of a November 2004 Pharmaceutical Advisory Committee report, relabeled warfarin to describe the pharmacogenetic factors that affect warfarin dose (Box 3).

The presence of the 2C9*2 and/or *3 variations in approximately a third of patients of European origin has a profound effect on the pharmacoki-

Box 3. The case for warfarin DNA testing

More than 30 million warfarin prescriptions are filled each year.

According to the FDA, hemorrhage during warfarin therapy is a leading cause of death in Western countries and related adverse events account for 1 in 10 hospital admissions.

Testable genetic variants are found in approximately half of patients and are the major contributor to the 40× variation in warfarin dose requirement.

Cytochrome P450 2C9 is the most important enzyme in the metabolism of warfarin and greatly affects the half life and time to a stable dose. Without genetic testing, it is not known if international normalized ratios test results represent a steady state or one that is climbing.

Vitamin K receptor, VKORC1, is the site of action of warfarin. The level of the enzyme is under genetic control according to the DNA sequence present in the control region of the gene. The more receptor present, the more warfarin required.

Routine DNA testing of 2C9 and VKORC1 in warfarin patients is predicted to prevent 85,400 bleeding events, 17,100 strokes and save US\$1.13 billion annually [10].

Table 2. Effect of CYP2C9 genotype on time to stable dose.

| CYP2C9 genotype | Time to stable dose (days) |
|--|----------------------------|
| *1/*1 extensive (normal) metabolizer | 4–5 |
| *1/*2 intermediate metabolizer | 8–10 |
| *1/*3, *2/*2, *3/*3 intermediate or poor metabolizer | 12–15 |

Data from [20].

netics of warfarin (Table 2). Patients carrying one or both of these alleles, and beginning warfarin therapy have double the risk of serious and life threatening bleeding events – the second most common medical reason for an emergency room visit [13,14].

Together variations in VKORC1, the target for warfarin action and 2C9 genetic status explain approximately one-half the variation seen in individual warfarin dose requirement. Another third is determined by age (-8% per decade), body surface area (-13% per standard deviation decrease), vitamin K intake and concomitant medications which are inhibitors of 2C9 (e.g., -20% amiodarone, -12% simvastatin) [15,16].

Several warfarin dosing algorithms are available that combine 2C9 and VKORC1 DNA test results with a variety of clinical factors to estimate a starting dose of warfarin [17,101]. Use of these algorithms predicts warfarin dose to within approximately 1 mg/d, a dramatic improvement to the trial and error methods in use today. Currently, the Sconce algorithm is integrated into GeneMedRx.

Future perspective

Pharmacogenetic research, especially of the cytochrome P450s, is at a fairly mature stage and believed by many scientists to be ready for application in the clinic [3]. Adoption of pharmacogenetic tests is beginning in a piecemeal fashion that will call into question one-size-fits-all, trial-and-error prescribing and lead to a more comprehensive approach to medication management. GeneMedRx can play an important role in enabling and driving this transition which will be helped by new DNA tests for pain management, choice of psychiatric medicines and others. Increased consumer access to drug management tools, information and testing will lead to more consumer centric healthcare which has the potential to be disruptive to a broad spectrum of healthcare enterprises. Diagnostics overtaking therapeutics leadership position could be as dramatic as the displacement of mainframe computers by PCs.

Financial & competing interests disclosure

Kristine Ashcraft and Howard Coleman are employed by Genelex Corp, Seattle, WA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Highlights

- Adverse medication outcomes including toxicity and treatment failure are a major public health problem.
- Wider use of genetic testing and software products available from Genelex could significantly reduce the morbidity, mortality and costs of adverse medication outcomes.
- GeneMedRx, enables physicians to optimize prescribing practices by correlating pharmacogenetic test results and patient medication regimens in the clinical setting.
- DNA testing for tamoxifen effectiveness and warfarin dosing are immediate opportunities for pharmacogenetic testing and personalized medication management to dramatically improve outcomes.
- Genelex seeks investment capital, strategic partners and licensing opportunities to widen the opportunities for comprehensive personalized medication management to improve healthcare outcomes.

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Website

101. Algorithm readily available on the internet www.warfarindosing.org